Feasibility of ultrasound cavitation agent mediated gastrointestinal drug delivery

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Background: In 1923, Harrison, a chemical pathologist in King's College Hospital, published a paper entitled "Insulin in alcoholic solution by the mouth". After 100 years of chemical and formulation research, formulation scientists still struggle to deliver biopharmaceuticals via the most convenient administration route due to the physiological barriers posed by the gastrointestinal tract which result in poor stability and permeability of biopharmaceuticals. Ultrasound mediated gastrointestinal drug delivery was inspired by the success of physical approaches in transdermal drug delivery research. This study explores the feasibility of ultrasound cavitation agent mediated gastrointestinal drug delivery in pursuit of the goal to deliver biopharmaceuticals via the oral route.

Methods: Lipid shell microbubbles were manufactured using a tissue homogeniser and were centrifugally washed to remove PBS and unincorporated lipid components. Microbubbles were then reconstituted in the relevant simulated fasted or fed state gastrointestinal media. Microbubble diameter and concentration were measured at 0, 1, 2, 3, 4, 5, 6 and 24 hours using electrozone sensing to assess gastrointestinal stability. Microbubbles were exposed for 1 minute to focused ultrasound of 0.5 MHz or 1.1 MHz frequency (sine waveform), 1000 cycles, 200 ms burst period, pulse repetition frequency of 5 Hz, and 1% duty cycle at peak negative pressures of 0.5, 1, and 2 MPa to assess acoustic response in gastrointestinal fluids. HIFU Franz cell were manufactured with clear acrylic resin, specifically Formlabs Clear Resin, using SLA 3D printing with a Formlabs 3B SLA printer. The acoustic field inside the HIFU Franz diffusion cell was determined using a fibre optic hydrophone. Ultrasound cavitation agent mediated gastrointestinal drug delivery was assessed by mounting porcine ileal or caecal tissues in the HIFU Franz cell, stimulating microbubbles with ultrasound, co-administering with a model large molecular weight drug, FITC-dextran 70 kDa, and then measuring: (i) change in tissue integrity of the tissue using TEER, (ii) acoustic response of microbubbles using PCD, and (iii) tissue uptake and apical to basolateral flux of FITC Dextran 70 kDa using fluorescence intensity using a plate reader.

Results: The stability of lipid-shelled microbubbles was demonstrated in fasted and fed state simulated gastrointestinal media. The acoustic response of microbubbles was examined in simulated gastrointestinal fluids, and results showed that fed state fluids diminished the acoustic response (0.5 and 1.1 MHz, 0.5, 1, 2 MPa peak negative pressure) A submergible HIFU Franz diffusion cell was developed that was compatible with TEER probes, HIFU ultrasound stimulation and passive cavitation detection, with minimal distortion of the sound field. The HIFU Franz facilitated the assessment of a standard microbubble formulation co-administered with FITC-dextran 70 kDa and found no alteration of the tissue integrity. Moreover, stimulation with ultrasound did not promote FITC-dextran 70 kDa uptake or permeation across biosimilar mucus covered porcine ileal/caecal tissue.

Conclusions: This study demonstrated stability of microbubbles in simulated gastrointestinal fluids, diminished acoustic response of microbubbles in fed state simulated gastrointestinal fluids, developed a submergible acoustically transparent Franz cell and demonstrated that microbubbles, under the investigated ultrasound settings, did not promote FITC-dextran 70 kDa tissue uptake or permeation. This study lays the foundation for future research to investigate new ultrasound parametric design spaces and new formulations to further progress towards ultrasound cavitation agent mediated gastrointestinal drug delivery.